themselves multiple dependent claims. In addition, the Examiner noted that Claims 14 and 15 are drawn to a cell line and vector, respectively, yet they depend from Claims drawn to a method. The claim amendments presented above address these objections. There are no longer any multiple dependent claims and claims 19 through 32 are now drawn solely to cell lines.

REJECTION UNDER 35 U.S.C. §112(1)

The Examiner has rejected claims 1 through 13 and 16 under 35 U.S.C. §112(1) as encompassing subject matter that is not described in such a way as to enable one skilled in the art to make and use the invention. The Examiner argues that the specification does not provide enough guidance with respect to dosage amount, dosage frequencies, modes of delivery, appropriate expression levels, or targeting to enable treatment of diabetes. Furthermore, the Examiner focuses on the unpredictability of the gene therapy art to support an argument that the present specification does not provide enough guidance to a person of skill in the art to make and use the invention.

The Federal Circuit has held that a patent specification complies with the enablement requirement as long as "undue experimentation" is not required to practice the invention. *In re Wands,* 858 F.2d 731 (Fed. Cir. 1988). The court has set forth a number of factors to consider in deciding whether a disclosure would require undue experimentation. These factors include:

1) the quantity of experimentation necessary;
2) the amount of direction or guidance presented;
3) the presence of absence of working examples;
4) the nature of the invention;
5) the state of the prior art;
6) the relative skill of those in the art;
7) the predictability or unpredictability of the art; and
8) the breadth of the claims.

Id.; Enzo Biochem., Inc. v. Calgene, Inc., 188 F.3d 1362

(1999). Applicants respectfully traverse the Examiner's rejection. A proper characterization of the predictability of the gene therapy art coupled with a review of some of the additional factors listed by the Federal Circuit as well as a discussion of Applicants' own successes support the proposition that if any experimentation is needed to practice the invention beyond that described in the Specification, it would not be "undue experimentation."

The amended claims are directed primarily to cell lines that can be used for *ex vivo* gene therapy. The Examiner's enablement rejection did not include original claims 14 and 15 which are directed to host cells and vectors; thus, amended claims 19 through 32 are similarly enabled.

Amended claims 33 and 34, however, are directed to a method of treating diabetes using *ex vivo* or *in vivo* gene therapy. In considering whether these claims are enabled, the Examiner has mischaracterized the predictability of the art. The Examiner cites several publications and quotes excerpts that seem to highlight the unpredictability of the gene therapy art. These cited publications, however, actually suggest just the opposite.

At the time of filing the present application, it had been 7 years since the first human subject underwent gene therapy for the treatment of severe combined immunodeficiency. Ross et al. (1996) *Human Gene Therapy*, 7:1781-1790. During those 7 years dramatic advances have been made and there have been numerous successes. In the Ledley article cited by the Examiner, the author notes that "[t]here is growing confidence that gene therapy will provide important pharmaceutical products in the next decade." Ledley, F.D. (1996) *Pharmaceutical Res.* 13:1595.

Ledley also notes that more than 150 clinical trials were underway in the United States and Europe in 1996 and that those trials have demonstrated that genes can be successfully introduced into patients by numerous methods and will express therapeutic proteins. *Id.* *See also,* Nabel, G. et al. (1993)

Proc. Natl. Acad. Sci. 90:11307-11311; Caplen, N.J. et al. (1995) *Nature Med.* 1:39-46; Zabner, L.A. et al. (1993) *Cell* 75:207-216; Grossman, M. et al. (1995) *Nature Genetics* 6:335-341; Gross, M. et al. (1995) *Nature Med.* 1:1148-1154. Numerous specific evidences of success are also discussed in Ledley. These include both cell-based and viral-based therapies. Some of those successes include attempts to treat ADA deficiency, LDL receptor abnormalities, Gaucher disease, AIDS, cancer, and arthritis.

The Crystal article also cited by the Examiner provides that "the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible. Although gene transfer has not been demonstrated in all recipients, most studies have shown that genes can be transferred to humans whether the strategy is *ex vivo* or *in vivo*, and that all vector types function as intended." Crystal, R.G. (1995) *Science* 270:405. Table 1 summarizes numerous studies wherein the transfer of genes to humans is feasible.

In the present case, GLP-1 is an ideal molecule to deliver through gene therapy. Many of the "hurdles" pointed out by the Examiner deal with ineffective delivery vectors, problems with targeting a specific cell, and problems with maintaining a level of expression that provides a therapeutic benefit. Diabetics, however, are not generally deficient with respect to endogenous GLP-1 production and thus, the goal is not to replace a defective gene but only to increase the levels of GLP-1 normally present. Thus, these so-called hurdles are not hurdles for the present invention.

On p. 408, Crystal discusses two types of therapeutic studies that support the biologic concept that minimal correction of a genotype can have significant phenotypic consequences. A liver biopsy several months after an *ex vivo* study involving retrovirus-mediated transfer of the LDL receptor cDNA indicated that at most 5% of the total hepatocyte population in the biopsy expressed the transferred

gene. "Despite this minimal correction, in some of the recipients there were changes in LDL-related parameters that suggested LDL receptor function in the liver had been partially restored." Similar results have been obtained through transfer of the CFTR cDNA to treat cystic fibrosis.

GLP-1 is produced endogenously from the L-cells of the intestine as part of a larger precursor protein that is proteolytically processed. Processed GLP-1 binds a specific receptor present on β-cells of the pancreas. GLP-1 that is administered by subcutaneous or i.v. injection has the effect of enhancing insulin secretion and inhibiting glucagon as well as other effects. Most importantly, GLP's activity is glucose dependent. If serum glucose levels rise above a threshold level in the blood GLP is able to exert an effect, however, if glucose levels fall, GLP can no longer function. Thus, there is no danger of hypoglycemia even with increased levels of GLP. Furthermore, even a small increase in GLP levels can be beneficial to a person with hyperglycemia. As long as GLP is secreted into the blood from an implanted expressing cell or a cell transformed *in vivo*, it will have the desired effect of reducing glucose levels. Thus, an investigator has both a choice of target cells as well as a choice of cells to implant depending on the type of therapy employed.

The Specification provides sufficient guidance to enable a person skilled in the art to practice the present invention. The Specification describes stable cell lines, expression vectors, DNA sequences, linker construction, transfection methods, as well as a transplantation protocol (See Example 7). Furthermore, following the methods provided in the Specification, Applicants have successfully transplanted GLP-1 secreting cells under the renal capsule of Zucker Diabetic Fatty (ZDF) rats (see Example 7) and, most importantly, a glucose lowering effect was observed following transplantation.

Contrary to the Examiner's assertion, both native GLP-1 as well as the GLP-1 analogs encompassed by the present

invention have therapeutic value. The short half-life associated with native GLP is due to degradation by the endogenous protease DPP IV. Despite this short half-life, native GLP-1 is clearly efficacious especially when administered by continuous infusion. See WO 98/08873. Furthermore, the analogs with changes at residue 8, as specifically defined in Claim 1, are DPP IV resistant which results in an increase in *in vivo* half-life.

The current clinical trials and resultant successes indicate that it is reasonable to extend successes in a non-human animal to humans. Furthermore as discussed above, efficiency with respect to number of expressing cells successfully transplanted and/or number of cells transfected *in vivo* is not critical for the present invention to have value from a therapeutic standpoint. Any increase in GLP concentration will be beneficial. Increases in GLP levels will result in enhanced endogenous insulin expression and thus, reduce the amount of insulin that a patient must self-administer. Reducing the amount that must be injected, the number of injections, or eliminating injections all together would clearly provide a benefit to diabetics.

Thus, based on the predictability of the art after 7 years of gene therapy clinical trials, the guidance provided in the specification, and applicants' successful transplantation of GLP-1 expressing cells, a person of ordinary skill in the art would not have to undergo undue experimentation to practice the invention as claimed.

REJECTION UNDER 35 U.S.C. §112(2)

The Examiner rejected Claims 1, 10, and 16 through 18 under 35 U.S.C. §112(2) as being indefinite. Specifically, the Examiner points to the term "immunologically isolated" as being vague and indefinite. This term, however, is discussed in the Specification (line 30, p. 10 through p. 11) and is well-known in the art. The present Specification provides that foreign cells can be protected from the recipients immune

system by masking them with $F(ab')_2$ fragments specific for HLA class I antigens. This masking procedure is how the cells are "immunologically isolated" from the patients immune system. Several citations are provided on page 11 of the Specification referencing immunological isolation methods.

The Examiner has also rejected various claims for improper Markush language. The amended claims are now consistent with accepted Markush language. In addition, Applicants have deleted the omnibus claims (16 - 18) from the amended claim set.

REJECTION UNDER 35 U.S.C. §102

The Examiner rejected Claims 14-15 and 16-18 as being anticipated by WO 90/01540 (hereinafter, Hilliker). Hilliker teaches that truncated CAT sequences fused in-frame to a mammalian protein such as GLP-1 can increase the yield of protein when expressed in a bacterial system. The Amended claims are now directed specifically to implantable host cells. Host cells encompassed by the present invention must be capable of being implanted into a mammal and must secrete a protein of SEQ ID NO. 1. Bacterial cells are not candidates for *ex vivo* gene therapy. Furthermore, the CAT-GLP fusion described in Hilliker does not result in a GLP protein that is secreted from the cell. The fusion must be isolated from a cell lysate and then cleaved to remove CAT. A non-secreted CAT-GLP fusion is not encompassed by the present claims. Thus, Applicants respectfully request the Examiner to withdraw this rejection as the amended claims do not encompass the subject matter disclosed in Hilliker.

SUMMARY AND CONCLUSION

In view of the remarks and amendments provided herein above, it is respectfully submitted that the rejections have been overcome. Reconsideration and withdrawal of the rejections are therefore requested.

If the Examiner feels that a telephone conversation with

Applicants' Attorney would be helpful in expediting the prosecution of this case, the Examiner is urged to call Applicants' Attorney at (317) 276-0280.

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